



Memorandum

Medical & Registration Department

From: Dr. Claudia Bobillier
Date: Dr. Ulrich Martin
15 May 1996

To: Mr. I. Claydon (by fax)
Dr. P. Goldenheim
Dr. W. Fleischer
Mr. K. Howell
Dr. R. Kaiko (by fax)
Dr. P. Kuster
Mr. P. Manners
Dr. A. J. Miller
Dr. R. B. Miller
Dr. Richard Sackler (by fax)
Mr. W. Wimmer

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P. Goldenheim, MD.

[Handwritten signature]

Minutes of the Meeting with Prof. Dayer in Geneva, 6. May 1996 OxyContin

Present: Prof. P. Dayer, Dr. J. Desmeules, Dr. V. Piguet (Pharmacology group of the Geneva University Hospital)
Dr. R. Kaiko (PF USA), Dr. U. Martin (MPCO, Switzerland), Dr. C. Bobillier (MPCO, Switzerland)

The meeting took place at the office of Prof. Dayer in the Geneva University Hospital.

R. Kaiko gave an excellent and very competent presentation of the kinetic and clinical data of OxyContin accompanied by the presentation of the data on slides. This formed the basis of a very profitable discussion and Prof. Dayer and his colleagues appeared to be impressed and indicated their interest by raising questions during the presentation. After the presentation the discussion continued and Prof. Dayer said he would be interested in participating in a study with OxyContin. However, the collaboration has to be initiated before the submission of the registration dossier. During the registration process of the product Prof. Dayer would not be willing to be involved in any study with us.

A good cooperation with Prof. Dayer, a most important person in the Swiss medical area, is decisive for the future. Since the meeting was very constructive for both sides, with an important exchange of knowledge and ideas, we came away with a positive impression.

We would also like to thank Robert Kaiko very much for coming to Switzerland and his much appreciated cooperation in this matter.

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Der Umwelt zuliebe..

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IN COMMONWEALTH OF KENTUCKY, EX REL. JACK CONWAY, ATTORNEY GENERAL v. PURDUE
PHARMA L.P., ET AL., CIVIL ACTION NO. 07-CI-01303 (PIKE COUNTY CIRCUIT COURT)

DEPOSITION
EXHIBIT

Sackler 37

The following main subjects were discussed after the presentation of the OxyContin data:

Prof. Dayer asked if steady state kinetics of oxymorphone are available. Although rigorously designed steady-state studies in normal volunteers assessed the kinetics of only oxycodone, there should be sufficient oxymorphone data from the steady-state studies in patients to answer the questions of interest.

Kaiko

Regarding the study "pharmacokinetic-pharmacodynamic relationship of CR oxycodone", Prof. Dayer wondered if the significant correlation between the pharmacodynamic variables and the oxycodone concentration, but not the oxymorphone concentration, could depend on the highly different concentrations of oxycodone and oxymorphone. This might influence the value of the correlation. He supposed that the drug effect values (e.g. pupil size) shown for oxymorphone could also be significant, if the correlation was not calculated with the absolute concentrations.

Kaiko

Prof. Dayer missed a pain indicating parameter in this study.

Due to the importance of the issue to Prof. Dayer and as agreed upon with Dr Martin in advance of the meeting, R. Kaiko mentioned the Finnish kinetic study from Kalso investigating the influence of quinidine on the metabolism of oxycodone. R. Kaiko undertakes to provide Prof. Dayer with a copy of the protocol and the results.

Kaiko

Prof. Dayer was interested in the data from the studies in renal and hepatic impairment.

Prof. Dayer asked if chronic tox data of the metabolites were available. (Not an essential point for a submission for registration.)

He was interested in data on receptor binding- and affinity-studies of oxycodone for the knowledge of mode of action of oxycodone and/or metabolites.

Kaiko

Regarding the clinical data Prof. Dayer mentioned that the indication "low back pain" is not regarded a suitable indication for opioids in Europe. This indication is accompanied by a psychological factor which holds a risk for addiction if opioids are used for treatment. On the other hand Prof. Dayer acknowledged that patients with pain secondary to osteoarthritis may be candidates for OxyContin.

He was very interested about the Canadian study in diabetics with neuropathic pain. Mr. Desmeules is working with these pain situations and is very much interested in the results.

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It was also discussed if a further analysis of the data from the study in patients with osteoarthritis could be made. If oxymorphone is the active compound (which is Prof. Dayer's opinion) a group of patients would not have sufficient analgesia under OxyContin. Undertaking a re-evaluation, results that are typical for poor metabolisers can most probably be detected and an additional phenotyping or analysis of oxymorphone in plasma should give further information. This very interesting point and excellent idea was taken up by R. Kaiko and he will undertake to initiate the necessary analyses.

Kaiko

Prof. Dayer did not see any major problems regarding registration of OxyContin in Switzerland. Some specific points need to be clarified (monitored release approval, as for DHC, may be a possibility).

He considers the following subjects as important and which would need further investigations:

- information about the abuse/addiction potential vs other opioids because of the rapid onset of action of OxyContin
- the interaction with the enzyme CYP4502D6
- clarification about the active compound(s)
- dose-finding: which dose for which disease for which patient

Prof. Dayer and his group are interested in doing a study with OxyContin and we agreed to discuss on both sides a possible outline.

Dayer
group,
Kaiko,
UMa, BC

The group should be provided with
OxyContin tablets + certificate of analysis,
Oxymorphone, oxycodone and noroxycodone powder - all with certificates of analysis.

UMa,
BC

With kind regards,



Dr. U. Martin
Head of Medical Department



Dr. C. Bobillier
Registration Manager

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